## Remarks/Arguments

The present amendment amends claims 20 and 21 to indicate "performed". The examiner noted in the previous response that term "preformed" was used and, from context of the term, presumed that the intended term is "performed".

*35 U.S.C. § 112, Second Paragraph (Essential Steps)*

Claims 1-8 and 18-25 stand rejected as allegedly lacking essential steps. The examiner argues the claims: (1) fail to recite a nexus between the difference in caspase 3 activity and the determination of viral stability and potency; (2) fail to provide a particular incubation time; and (3) fail to set forth a standard or fixed evaluation condition. These rejections are respectfully traversed.

(1) Nexus Between Caspase 3 Activity Differences and Viral Stability and Potency

Claim 1 refers to measuring caspase 3 activity as an indication of viral activity in a formulation or different formulations. The difference in caspase 3 activity for a virus taken from a first and second formulation is indicated in claim 1 to provide an indication of virus stability and potency in the first formulation compared to the second formulation. The difference in caspase 3 activity for a virus taken from a first formulation at two or more time intervals is indicated in claim 1 to provide an indication of virus stability and potency in the first formulation.

The examiner asks whether viral stability and potency is present, absent, significant, insignificant, substantial or insubstantial when caspase 3 activity is more or less in one formation compared to another. The rejection goes to how the results of the assay are interpreted and not to an essential step for performing the assay itself.

As indicated in the claims, the difference in activity provides an indication as to viral stability and potency. The present invention is not based on how magnitudes of difference in activity are treated by the skilled artisan. Such an evaluation is readily within the ability of one of ordinary skill in the art.

(2) Incubation time

The examiner argues that the application at page 9, lines 9-10 promotes the use of a 1-hour incubation period for caspase 3 activity. While a 1-hour incubation time is preferred, the application does not refer to a 1-hour incubation time as critical.

The application provides data illustrating that a particular incubation time is not critical. In the same paragraph noted by the examiner, the application mentions that for measles virus the assay is linear for "at least" one hour, and for mumps virus the assay is linear for "at least" 75 minutes. (The present application at page 9, lines 1-10.)

(3) Standard or Fixed Evaluation Conditions

The examiner argues that the claims lack reference to a standard or fixed evaluation condition and such a limitation is necessary for a meaningful analysis. The examiner fails to indicate where the application references a standard or fixed evaluation conditions as an essential part of the invention.

Standard or fixed evaluation conditions might be preferred for performing an assay. However, such conditions are not "essential". For example, the skilled artisan can perform the assays under different conditions where there is some variability in the assay results and still obtain meaningful information. Adjusting conditions for performing an assay, and effect of changing a particular condition, is well within the ability of the skilled artisan.

*35 U.S.C. § 112, Second Paragraph (New Matter)*

Claims 21 and 24 stand rejected as allegedly providing new matter. The examiner argues that the application does not support reference to removing the virus from a formulation at two or more time intervals. The rejection is respectfully traversed.

Support for claims 21 and 24 is provided, for example, on page 1, lines 23-26, page 5, lines 13-14 and original claim 7. The application on page 1, lines 23-26, includes reference to assaying caspase 3 activity for measuring viral potency and stability. The application on page 5, lines 13-14 points out that the caspase 3 assay is preferably employed on viral vaccine samples either in liquid or lyophilized form. Original claim 7 ultimately relates back to claim 1 and refers to repeating steps (a) and (b) at two or more time intervals. Steps (a) and ( b) originally

recited in claim 1 are: (a) contacting a plurality of cells susceptible to caspase 3 induction with said virus; and (b) measuring caspase 3 activity as an indication of viral stability.

*35 U.S.C. § 102 (Claims 1-3 and 7)*

Claims 1-3 and 7 stand rejected as allegedly anticipated by Banki et al. (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953.) The examiner argues Banki et al. teaches the active steps of (a) contacting cells susceptible to caspase 3 induction with a virus, wherein the virus induced caspase 3 activity, and (b) measuring said caspase 3 activity, wherein steps (a) and (b) are repeated at two or more time intervals. The examiner refers to Banki et al. at page 11946, Figure 2, with caption; page 11948, 1st sentence, last full paragraph; and page 11949, Figure 5 with caption. The rejection is respectfully traversed.

The Banki et al. sections noted by the examiner fail to repeat both steps (a) and (b). Instead of repeating step (a), Banki et al. describes a continuous time-course for measuring HIV induced apoptosis. Banki et al. initially infects a set of cells, then at different times measures apoptosis from the initially infected cells.

*35 U.S.C. § 103 (Claims 4, 5, 18, 19)*

Claims 4, 5, 18 and 19 stand rejected as allegedly obvious based on Banki et al. in view of Duncan et al. (Virology 255, 117-128, 1999). Duncan et al. is cited for teaching Vero and RK13 cells are susceptible to caspase 3 activity and that rubella induces caspase 3 activity. The examiner argues that Duncan et al. is deficient in not teaching measurement of caspase 3 activity and that one skilled in the art would be motivated to combine Banki et al. with Duncan et al. to quantify viral induced apoptosis. The rejection is respectfully traversed.

Duncan et al. teaches measuring apoptosis in general by quantifying detached cells. The proposal to modify Duncan et al. to measure caspase 3 activity as indication or viral activity is inconsistent with Duncan et al. looking for effects caused by apoptosis in general.

Duncan et al., is not concerned with measuring viral activity. Duncan et al. concerns studying the cellular basis of the ability of the rubella virus to cause system birth defect in the fetuses of infected women. (See Duncan et al. abstract, first two sentences.) Duncan et al. indicates that other caspases, in addition to caspase 3, are involved the observed apoptosis. (Duncan et al., at page 125, first column, third paragraph.)

Banki et al. measures caspase 3 activity to study HIV induced apoptosis. Banki et al. fails to provide motivation to modify Duncan et al. to specifically look at caspase 3 activity alone or in combination with other particular caspases, as an indication of viral activity.

*35 U.S.C. § 103 (Claim 6)*

Claim 6 stands rejected as allegedly obvious based on Banki et al. as applied to claims 1-3 in view of Wu et al. (provisional application 60/108606, priority document to U.S. Patent No. 6,689,600). Wu et al. is cited for teaching that lyophilization improves stability of viral vaccine and recombinant proteins. This rejection is respectfully traversed.

Claim 6 depends from claim 1. As noted above, claim 1 distinguishes Banki et al., for example, by indicating steps (a) and (b) are repeated at two or more time intervals. Wu et al. fails to cure the deficiencies in Banki et al.

*35 U.S.C. § 103 (Claim 8)*

Claim 8 stands rejected as allegedly obvious based on Banki et al. as applied to claims 1-3 in view of Goodrich et al. (U.S. Patent No. 5958670). Goodrich et al. is cited for teaching a method of storing cells by freezing and later thawing. This rejection is respectfully traversed.

Claim 8 depends from claim 1. As noted above, claim 1 distinguishes Banki et al., for example, by indicating steps (a) and (b) are repeated at two or more time intervals. Goodrich et al. fails to cure the deficiencies in Banki et al.

*35 U.S.C. § 103 (Claim 22)*

Claim 22 stands rejected as allegedly obvious based on Banki et al. in view of Esolen et al. (Journal of Virology, June 1995, p. 3955-3958). Banki et al is cited for teaching a method of measuring caspase 3 activity to quantify virally induced apoptosis. Esolen et al. is cited for teaching that measles virus induces apoptosis. The examiner argues it would be *prima facie* obvious to combine Banki et al. with Esolen et al. to quantify apoptosis induced by measles virus.

Esolen et al. is not concerned with determining viral activity. Esolen et al. is directed to determining the mechanism of measles virus-induced cell death. (See Esolen et al. abstract on page 3955.) Esolen et al. notes that DNA fragmentation indicative of apoptosis was apparent by

flow cytometry, agarose gel electrophorese and election microscopy. (See Esolen et al. abstract on page 3955.)

The skilled artisan would not be motivated to modify Esolen using the methods employed by Banki et al. to determine the mechanism of measles virus-induced cell death. Esolen et al. does not reference caspase 3 activity as involved in the observed cell death or indicate that caspase activity should be quantified.

*35 U.S.C. § 103 (Claims 1, 20, 23 and 25)*

Claims 1, 20, 23 and 25 are allegedly obvious based on Banki et al. as applied to claim 18 in view of Wu et al. The rejection is directed to reference in the claims to measurement of caspase 3 activity from two different formulations. Banki et al. is cited for teaching a method of measuring caspase 3 activity to quantify viral induced apoptosis. Wu et al. is cited for teaching the significance of formulations on biological activity. The examiner argues that one of ordinary skill in the art would be motivated to determine the effect of the formulation on the biological activity and structural integrity of the virus.

The rejection fails to indicate particular modifications to Banki et al. or Wu et al. Instead the rejection generally alleges the two references should be combined to provide an assay to determine the effects of a formulation on viral activity.

The fact that formulations can affect viral activity, does not provide motivation to measure caspase 3 activity as an indication of viral activity in different formulations. Banki et al. concerns studying HIV induced apoptosis. Banki et al. does not indicate that caspase 3 activity should be measured to provide an indication of viral activity in a particular formulation. Wu et al. fails to cure such deficiencies.

Please charge deposit account 13-2755 for fees due in connection with this response. If any time extensions are needed for the timely filing of the present response, applicant petition for such extensions and authorize the charging of deposit account 13-2755 for the appropriate fees.

Respectfully submitted,

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